Our Reference No. 2223-171

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.: 5362

Appl. No. : 10/731,741
Applicants : Schmitt et al.
Filed : December 10, 2003
Title : Cell Preparations Comprising Cells of the T Cell Lineage and Methods of Making and Using Same.
TC./A.U. : 1632
Examiner : Anoop Kumar Singh

Docket No. : 2223-171
Customer No. : 001059

DECLARATION UNDER 37 C.F.R. 1.132

Honourable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Charles D. Surh citizen of the United States of America and resident of California declare that the following facts are within my knowledge and are true.

1. I am a Professor of Immunology at the Scripps Research Institute. I am a leading authority on the immune system and the role of T lymphocytes. I am especially noted for my work on the selection of young T cells in the thymus and the factors controlling mature T cell survival in the extrathymic environment.

My curriculum vitae is attached as Exhibit A.

2. I have reviewed the above-referenced application (hereinafter "the application") and the Office Action for the application that issued on October 27, 2008.

3. In particular, I note the Examiner's objection the claims as being obvious over a combination of the references Jaleco et al. (2001, J. Exp. Med. 194:991-1001, IDS); Nakano et al. (1994, Science 265:5157 IDS); Pui et al. (Immunity, 1999, 11(3):299-308), and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS). I respectfully disagree with the Examiner for the reasons that follow.

4. It is my utmost professional view that the invention described in the application that OP9-DL1 cells support T cell development is original and its novelty and inventiveness is NOT negated by prior publications. The closest prior art is found in a publication by Jaleco et al in 2001 who claimed that S17-DL1 cells induced differentiation of human cord blood progenitors cells into T cells. Careful examination of this paper, however, reveals that this conclusion is a great over interpretation of their results, mostly contained in Table 1. In their experiments Jaleco et al cultured progenitor cells for up to 6 wks with S17-DL1. Their strongest data are that at 4 and/or 6 wk time points they found cells displaying T cell markers: surface expression of CD7 (76-82%), CD4/8 (2-4%), CD3 (2-4%) and cytoplasmic expression of CD3

(66.2%). I am NOT convinced that any of these data are unequivocally proof of T cell development for the following reasons. First, the starting progenitor cell populations were only 87% pure and contaminated with cells expressing T cell markers (10% CD7, 5% CD3); hence, these contaminating cells could have persisted and expanded over 4-6 wks. The duration of 4-6 wks is also much longer than the 2 wks that is typically required for T cell development in vivo (and in vitro as shown by the inventors' work), indicating that S17-DL-1 cells were extremely inefficient at promoting T cell development and/or contaminating cells expanded during this time. Second, cells expressing immature T cell markers, CD4/8 (2-4%), could reflect activated $CD3^+$ mature T cells (5% in the starting population), as it is known that activated human T cells often express both CD4 and CD8. Third, surface CD7 and cytoplasmic CD3 expression cannot be used as a T cell-specific marker as human NK cells also express these markers. The only way to circumvent these concerns is to start with highly pure progenitor cells, void of mature T cells, and analyze several T and NK cell markers on the recovered cells by multiple-color staining. Since these approaches were not taken, the data by Jaleco et al cannot be accepted as proof that expression of Delta-1 on stromal cells induces differentiation of progenitor cells into immature T cells. This skepticism is especially relevant in light of many previous false claims of cell lines that were touted to support T cell development in tissue cultures. Hence, such weak data by Jaleco et al were not considered by me and most other T cell biologists to be a definitive demonstration that Delta-like-1 on a

cell line can promote T cell development. This notion is further underscored by the fact that no one has since published a report confirming that S17-DL1 cell lines can support T cell development.

The inventors, by contrast, used progenitor cells purified from mouse day 14 fetal liver cells, which are known to not contain any immature or mature T cells. Their OP9-DL1 cells induced generation of huge numbers of cells with a high proportion (>50%) of cells expressing all the known markers of immature and mature T cells in about 2 wk. The use of OP9 cannot be considered obvious as OP9 cells were originally generated to facilitate the differentiation of stem cells to various lineages of hematopoietic cells other than macrophages, especially B cells, erythrocytes, and myeloid cells. Since T cells are not one of these lineages, and because a method for in vitro development of T cells was not known at that time, it was not obvious that OP9 was the cell of choice for promoting T cell development.

5. It should be noted that the requirement for Notch signaling for differentiation of progenitor cells into T cells was being described in the literature prior to work by the inventors. The role of Notch on T cell development was first investigated in the mid 1990s, but the real definite understanding did not emerge until 1999 from work by Radtke et al (Immunity, 1999, 10:547-558). Prior to this there was a lot of confusion. Moreover, Notch signaling is complicated by the presence of several ligands and

multiple molecules that regulate Notch interaction to its ligands and its intracellular signaling. Therefore, it is not obvious to use Delta-like-1 on OP9 cells, instead of using other Notch ligands or using one of the Notch signaling modulators.

6. Overall, I strongly feel that production of OP9-DL1 cells by the inventors is novel and inventive. This cell line has survived the test of time and has been the cell line of choice for studying T cell development under in vitro conditions. All other claims of similar feat have disappeared. Many other investigators had desired and attempted to generate a cell line like OP9-DL1, but no one else was able to, including Jaleco et al.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such a willful false statement may jeopardize the validity of the application or any patent issuing thereon.

January 11, 2009 _____ _____

Date Charles D. Surh

CURRICULUM VITAE

Charles D. Surh

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Title/Affiliation: Professor
Department of Immunology
The Scripps Research Institute

PERSONAL

Date of Birth: January 30, 1961
Place of Birth: Seoul, Korea
Citizenship: U.S.A.
Marital Status: Married with three children

EDUCATION

1978 - 1983 B.A., Chemistry, University of California, San Diego, California
1984 - 1989 Ph. D., Immunology, University of California, Davis, California

PROFESSIONAL RECORD

1989 - 1992 Postdoctoral Fellow, Department of Immunology,
The Scripps Research Institute, La Jolla, California.
Laboratory Head: Dr. Jonathan Sprent

1992 - 1993 Senior Research Associate, Department of Immunology,
The Scripps Research Institute, La Jolla, California

1993 - 1998 Assistant Professor, Department of Immunology,
The Scripps Research Institute, La Jolla, California

1998 - 2005 Associate Professor, Department of Immunology,
The Scripps Research Institute, La Jolla, California

2005 – 2008 Associate Professor with Tenure, Department of Immunology,
The Scripps Research Institute, La Jolla, California

2008 – present Professor, Department of Immunology,
The Scripps Research Institute, La Jolla, California

AWARDS AND HONORS

Student Research Prize from the 39th Annual Meeting of the American Association for the Study of Liver Disease, November 1988

Member of the Biological Science Council representing the graduate students of the University of California, Davis, 1988-1989

Special Fellow, Leukemia Society of America, July 1993 - June 1996

Scholar, The Leukemia and Lymphoma Society, July 1999 - June 2004

Ho-Am Prize in Medicine, 2007

INVITED PRESENTATIONS (from 1999)

04/19/1999	Experimental Biology '99 (FASEB) meeting, Washington, D.C., speaker and co-chair of Block Symposium on T Cell Development
09/13/1999	La Jolla Institute for Allergy & Immunology, Seminar Series, San Diego, CA
09/30/1999	The Scripps Research Institute, Immunology Affinity Group Seminar Series
10/04/1999	University of Washington, Immunology Seminar Series, Seattle, WA
10/18/1999	Second International Workshop on Antigen Processing and Presentation, Role of MHC Molecules in Selection and maintenance of T-Cell Repertoire Session, Bar Harbor, Maine
01/23/2000	Midwinter Conference of Immunologists at Pacific Grove, California, Differentiation and Cell Death in Lymphocyte Development Session
04/07/2000	Walter & Eliza Hall Institute, Melbourne, Australia, Immunology Seminar Series
04/11/2000	ThymOz III, an international workshop on T cells, speaker and co-chair at Peripheral T Cells Session
05/18/2000	University of British Columbia, Vancouver, Canada, Distinguished Lecture Series
05/23/2000	Emory University, Atlanta, Georgia, Immunology Seminar Series
05/24/2000	Medical College of Georgia, Augusta, Immunology Seminar Series
05/25/2000	NYU Medical Center, New York, NY, Immunology Seminar Series
02/20/2001	Gordon Conference on Immunochemistry and Immunobiology, Ventura, California, T cell Homeostasis Session
05/15/2001	Transplant 2001, The Joint American Transplant Meeting, Chicago, Illinois, Basic Science Symposium: Immune Regulation
07/25/2001	11th International Congress of Immunology, Stockholm, Sweden, co-chair of Workshop on Memory T Cells
10/23/2001	27th Annual Conference of the La Jolla Immunologists, La Jolla, CA, speaker and chair of session on Lymphocyte/Immune Cell Development
11/04/2001	ThymUs, an international workshop on T cells, speaker and co-chair of session on T Cell Homeostasis
01/26/2002	Midwinter Conference of Immunologists at Pacific Grove, CA, Control of Lymphocyte Survival Session

02/08/2002 9th International Conference on Lymphocyte Activation and Immune Regulation titled Lymphocyte Traffic and Homeostasis, Newport Beach, CA, Naïve T Cells Session
04/20/2002 Experimental Biology 2002 (FASEB) meeting, New Orleans, Louisiana, Major Symposium G on Homeostasis in the Immune System
05/20/2002 University of Minnesota at Minneapolis, Minnesota, MICaB Graduate Student Seminar Series
07/12/2002 Trudeau Institute, Saranac Lake, New York, Immunology Seminar Series
10/15/2002 NIH, Immunology Interest Group Seminar Series
12/03/2002 British Society for Immunology Congress, Harogate, England, Markers for Memory Session
01/07/2003 Keystone Symposia: Mechanisms of Immunologic Tolerance and Its Breakdown, Snowbird, Utah, chair of a workshop
01/30/2003 Keystone Symposia: Linking Innate with Adaptive Immune Responses, Immune Responses Plenary Session, Taos, NM
02/25/2003 Louisiana State University Health Sciences Center, Department of Microbiology, Immunology and Parasitology Seminar Series
04/01/2003 ThymOz IV, An International Workshop on T Lymphocytes, Co-chair and speak in T cell selection and Maturation session
04/28/2003 Oregon Health & Science University, Portland, OR Immunology Seminar Series
05/13/2003 University of Pennsylvania, Immunology Colloquium Series
05/15/2003 Yale University, Immunobiology Seminar Series
06/28/2003 FASEB Summer Research Conferences on Lymphocytes and the immune system: Molecular, Cellular and Integrative Mechanism, Regulation of Immune Responses session, Tucson, AZ
09/10/2003 NIH-Cytokine Interest Group Symposium, Cytokines and Lymphoid Homeostasis.
09/24/2003 The University of Iowa, Immunology Seminar Series
10/09/2003 The 15th Annual Meeting of the Korean Society of Molecular and Cellular Biology, Immunological Memory Symposium, Seoul, Korea
10/10/2003 The 33rd Annual congress of The Korean Society of Transplantation, , Seoul, Korea
11/19/2003 The University of Texas Southwestern Medical Center at Dallas, Excellence in Immunology Lecture Series
02/04/2004 10th DRDC-IBS Workshop on Stress and Immunity, Autrans, France, Lymphocyte population dynamics session
07/18/2004 12th International Congress in Immunology, Montreal, Canada, Co-chair and speaker in minisymposium on Lymphoid Homeostasis
09/16/2004 UCI Center for Immunology and UCI Cancer Research Institute, UC Irvine, Irvine, CA, Seminars in Immunology series.
03/19/2005 Keystone Symposia, Basic Aspects of Tumor Immunology, Keystone, CO, Cytokines and Chemokine session.
05/18/2005 Cleveland Clinic Foundation, Cleveland, OH, Department of Immunology Seminar Series.
05/22/2005 American Transplant Congress, Seattle, WA, Basic Science Symposium: T Cell Memory and Homeostasis.
06/11/2005 FASEB Summer Research Conference on Autoimmunity, Saxton River, VT, Chair and Speaker in Innate Immunity and Dendritic Cells in Autoimmunity Session.

09/25/2005 Aegean Conference of Autoimmunity, Santorini, Greece
10/27/2005 Frontier in Transplantation, Seoul National University Hospital, Seoul, Korea
10/27/2005 International Cytokine Society Conference 2005, Seoul, Korea, Symposium 7: Cytokines and Memories.
10/31/2005 Pohang University Seminar Series, Pohang, Korea
11/01/2005 Inaugural Symposium for Translational Research Center for Intractable Diseases, Ulsan University Hospital, Ulsan Korea
11/07/2005 Charles Gould Easton Seminar series, University of Toronto, Toronto, Canada
11/19/2005 Autumn Immunology Conference, Chicago, IL, Tumor Immunology Session
11/21/2005 Immunology Seminar Series, The University of Chicago Biomedical Science Cluster
03/06/2006 Seminar Series, Intercollegiate Faculty of Nutrition, Texas A & M University, College Station, TX
05/03/2006 Immunology Group Seminar Series, University of Maryland, Baltimore, MD
06/02/2006 7th Elsinore meeting on Infection Immunity, Immune Memory Session, LO-Skolen, Elsinore, Denmark
08/12/2006 FASEB Summer Conference in Lymphocytes and Antibodies, T cell homeostasis/memory session, Indian Wells, CA
11/08/2006 Symposium on T Cell Memory & Tolerance, POSTECH, Pohang, Korea
11/10/2006 Korean Association of Immunologist Conference, Memory T cells Session, Seoul, Korea
11/11/2006 Annual Symposium of Transplantation Research Institute, Seoul University, Seoul, Korea
02/27/2007 Johnson & Johnson PRD, San Diego, CA
03/03/2007 Keystone Symposium on Immunologic Memory, CD4^{+} T cell Memory Session, Santa Fe, NM
03/28/2007 Keystone Symposium on The potent new Anti-Tumor Immunotherapies, Lymphodepletion Session Chair and Speaker, Banff, Alberta, Canada
04/24/2007 Immunology Seminar Series, University of Miami, Miami, FL
04/30/2007 Immunology Forum, Dept. of Microbiology, Immunology & Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA
06/12/2007 Immunology Seminar Series, La Jolla Institute of Allergy and Immunology, La Jolla, CA
06/28/2007 SRC Summer Camp, Session on Immune Manipulation, Kang-Neung, Korea
08/29/2007 Novo Nordisk AS/ Malov, Denmark
10/04/2007 Perspectives in Melanoma XI, Session on Regulation of Immunity: Keys to Melanoma Therapy, Huntington Beach, CA
10/28/2007 Keynote Speaker, The Immunology Group of Victoria Annual Retreat, Beechworth, Australia
11/06/2007 Symposium on T Cell Memory, POSTECH, Pohang, Korea
11/09/2007 Korean Association of Immunologist Conference, Transplantation Session, Seoul, Korea
11/10/2007 Annual Forum on Xenotransplantation, Xenotransplantation Center, Seoul National University, Seoul, Korea
02/13/2008 Faculty Lecture Series, The Scripps Research Institute, La Jolla, CA

04/06/2008	Experimental Biology 2008, American Association of Immunology, Co-Chair of Block Symposium. San Diego, CA
06/02/2008	Ho-Am Lecture, Sung Kyun Kwan University, Suwan, Korea
08/14/2008	UKC2008, US-Korea Conference on Science and Technology, Chair and Speaker in Cell Signaling Session. San Diego, CA
09/03/2008	George Washington University, Microbiology Immunology and Tropical Medicine, Medical Center Dean Seminar Series, Washington, DC
09/26/2008	Frontiers in Immunological Memory, Division of Basic & Clinical Immunology, Univ. of Calif. At Irvine, Newport Beach, CA
10/23/2008	University of Massachusetts Medical School, Pathology Fall Seminar Series, Worchester, MA
11/09/2008	ThymUS, International Conference on Lymphopoiesis, T cell differentiation and Immune Reconstitution, San Juan, Puerto Rico
11/12/2008	Human Antibodies & Hybridomas 2008, New York, NY

JOURNAL RESPONSIBILITIES

1993-2005	Associate Editor, The Journal of Immunology
2008-2009	Associate Editor, Immunology, Journal of British Immunology Society

Ad hoc reviewer for Science, Nature, Cell, Immunity, Nature Immunology, Nature Medicine, Nature Reviews in Immunology, The Journal of Experimental Medicine, Proceedings of National Academy of Science, Journal of Immunology, Journal of Clinical Investigation, Blood and European Journal of Immunology

PROFESSIONAL ACTIVITIES

02/08/1998	Site Visit for NCI program project review, Seattle, WA
1999-2001	Study section grant review – American Heart Association, National Review Committee
04/12/2002	Special Emphasis Panel, Immunological Sciences Study Section, grant review, National Institutes of Health
2002-2003	Organizing committee for Annual La Jolla Immunology Conference
2003-2008	Science Advisory Board member for Xenotransplantation Research Center, Seoul National University Hospital, Seoul, Korea
09/12/2004	Site Visit, Laboratory of Mammalian Genes and Development, NICHD, NIH, Bethesda, MD
2004-2007	Science Advisory Committee member for Center for Children's Environmental Health, UC Davis, Davis, CA
2006-present	Committee that on evaluation new mutant mouse strains for repository, NIAID, NIH, Bethesda, MD

October, 2006	Ad hoc reviewer for CMI-B Study Section, NIH, Bethesda, MD
2006-2008	Chair of Immunology Affinity Group, TSRI
2004-2008	Scientific Committee for ThymUS'08, International Conference on Lymphopoiesis, T cell differentiation and Immune Reconstitution

TEACHING ACTIVITIES

07/23/2005	AAI Advanced Immunology Course, Stanford University, CA, Lecture on T Lymphocyte Homeostasis and Memory
07/20/2006	AAI Advanced Immunology Course, Stanford University, CA, Lecture on T Lymphocyte Homeostasis and Memory.
2007-	Participate in teaching the Immunobiology Course at TSRI Graduate program
07-08/2007	Teach a special 6-week Advance Immunology Course at POSTECH, Pohang, Korea
07-08/2007	Lecture at weekly faculty T-cell Meeting at Seoul National University, Seoul, Korea

PATENTS

Methods for increasing the biological Activity of Cytokines or Lymphokines for treatment of disease in a mammalian subject. PTC International Application filed 08/13/2008

CURRENT PERSONNEL

Jared Purton, Ph.D.
08/01/03-present
Previous position: Graduate Student
Monash University, Melbourne, Australia

Ester M.M. van Leeuwen, Ph.D.
03/12/06 – present
Previous position: Graduate Student
University of Amsterdam, Amsterdam,
The Netherlands

Mee Kum Kim, M.D.
03/2008 – present
Visiting Scientist from
Seoul National University Medical School
Seoul, Korea

Joonyoub Lee
05/01/04-present
Graduate Student, TSRI

Chris Martin
05/01/2007-present
Graduate Student, TSRI

David Kim
06/01/2003-present
Technician

PAST TRAINEES

Ted Burgardt
Technician
Current position: Veterinary school

Jennifer M. Chang
Undergraduate student, UCSD/Scientific Intern
Current position: Graduate Student
University of California, Berkeley

Walter L.S. Chang
Undergraduate student, UCSD/Scientific Intern
Current position: Medical School

Zhaoqing Ding
High School Student/Scientific Intern
Current Position: Graduate Student
Stanford Univeristy, Stanford, CA

Wolfgang Dummer, M.D.
Postdoctoral Fellow
Current position: Staff Scientist
Genentech, Inc.
South San Francisco, California

Bettina B. Ernst, Ph.D.
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Laboratory Manager
UMNW, ETH
Zurich, Switzerland

William Chad Kieper, Ph.D.
Postdoctoral fellow
Current position: Sr. Immunologist
3M Pharmaceuticals
St. Paul, Minnesota

Dong-Sup Lee, M.D., Ph.D.
Postdoctoral Fellow
Current position: Assistant Professor
Seoul National University
Seoul, Korea

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Poway, CA

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Postdoctoral fellow
Current position: Adjunct Professor
Moorpark College, Moorpark CA

Joyce Tsi Tan, Ph.D.
Postdoctoral fellow
Current position: Scientist
Pfyzer, Inc
San Diego, CA

Kien Vuu
Undergraduate student, UCSD/Scientific Intern
Current position: Resident in Radiology
University of California, Los Angeles

PUBLICATIONS (excluding abstracts)

1. Glassy, M. C., C. D. Surh, and S. Sarkar. Murine monoclonal antibodies that identify antigenically distinct subpopulations of human sperm. *Hybridoma* 3:363-371 (1984).

2. Glassy, M. C. and C. D. Surh. Immunodetection of cell-bound antigens using both mouse and human monoclonal antibodies. *J. Immunol. Methods* 81:115-122 (1985).

3. Gaffar, S. A., C. D. Surh, and M. C. Glassy. Variations in the secretion of monoclonal antibodies by human-human hybridomas. *Hybridoma* 5:93-105 (1986).

4. Glassy, M.C., H. H. Handley, C. D. Surh, and I. Royston. Genetically stable human hybridomas secreting tumor-reactive human monoclonal IgM. *Cancer Investigation* 5:449-457 (1987).

5. Surh, C. D., M. E. Gershwin, and A. Ahmed. A peripheral and central T cell antigen recognized by a monoclonal thymocytotoxic autoantibody from New Zealand black mice. *J. Immunol.* 138:1421-1428 (1987).

6. Surh, C. D., A. E. Cooper, R. L. Coppel, P. Leung, A. Ahmed, R. Dickson, and M. E. Gershwin. The predominance of IgG3 and IgM isotype antimitochondrial autoantibodies agaisnt recombinant fused mitochondrial polypeptide in patients with primary biliary cirrhosis. *Hepatology* 8:290-295 (1988).

7. Coppel, R. L., L. J. McNeilage, C. D. Surh, J. Van de Water, T. W. Spithill, S. Whittingham, and M. E. Gershwin. Primary structure of the human M2 mitochondrial autoantigen of primary biliary cirrhosis: dihydrolipoamide acetyltransferase. *Proc. Natl. Acad. Sci.* 85:7317-7321 (1988).

8. Surh, C. D., A. Ansari, and M. E. Gershwin. In vitro functional characterization of SAG-3 - A naturally occurring monoclonal antibody in NZB mice: specificity towards functional T cell subsets. *Hybridoma* 7:609-625 (1989).

9. Surh, C. D., D. J. Danner, A. Ahmed, R. L. Coppel, I. R. Mackay, R. Dickson, and M. E. Gershwin. Reactivity of primary biliary cirrhosis sera with a human fetal liver cDNA clone of branched alpha-keto acid dehydrogenase dihydrolipoamide acyltransferase, the 52 kD mitochondrial autoantigen. *Hepatology* 9:63-68 (1989).

10. Krams, S. M., C. D. Surh, R. L. Coppel, A. Ansari, B. Ruebner, and M. E. Gershwin. Immunization of experimental animals with dihydrolipoamide acetyltransferase, as a purified recombinant polypeptide, generates mitochondrial autoantibodies but not primary biliary cirrhosis. *Hepatology* 9:411-416 (1989).

11. Van de Water, J., C. D. Surh, P. S. C. Leung, S. M. Krams, D. R. Fregeau, P. Davis, R. Coppel, I. Mackay and M. E. Gershwin. Molecular definitions, autoepitopes and enzymatic activities of the mitochondrial autoantigens of primary biliary cirrhosis. *Sem. Liver Dis.* 9(2):132-137 (1989).

12. Van de Water, J., A. Cooper, C. D. Surh, D. J. Danner, R. L. Coppel, R. Dickson, and M. E. Gershwin. Detection of autoantibodies to recombinant mitochondrial proteins in patients with primary biliary cirrhosis. *New Eng. J. Med.* 320:1377-1380 (1989).

13. Surh, C. D., T. E. Roche, D. J. Danner, A. A. Ansari, R. L. Coppel, R. Dickson, and M. E. Gershwin. Antimitochondrial autoantibodies in primary biliary cirrhosis recognize cross-reactive epitope(s) on protein X and dihydrolipo-amide acetyltransferase of pyruvate dehydrogenase complex. *Hepatology* 10:127-133 (1989).

14. Surh, C. D., A. A. Ansari and M. E. Gershwin. Comparative epitope mapping of murine monoclonal and human autoantibodies to human PDH-E2, the major mitochondrial autoantigen of primary biliary cirrhosis. *J. Immunol.* 144:2647-2652 (1990).

15. Surh, C. D., R. Coppel and M. E. Gershwin. Structural requirement for auto-reactivity on human pyruvate dehydrogenase-E2, the major autoantigen of primary biliary cirrhosis: implication for a conformational epitope. *J. Immunol.* 144:3367-3374 (1990).

16. Van de Water, J., A. A. Ansari, C. D. Surh, R. Coppel, T. Roche, H. Bonkovsky, M. Kaplan and M. E. Gershwin. Evidence for the targeting by 2-oxo-dehydro-genase enzymes in the T cell response of primary biliary cirrhosis. *J. Immunol.* 146: 89-94 (1991).

17. Agus, D. B., C. D. Surh, and J. Sprent. Reentry of T cells to the adult thymus is restricted to activated T cells. *J. Exp. Med.* 173:1039-1046 (1991).

18. Karlsson, L., C. D. Surh, J. Sprent, and P. A. Peterson. A novel class II MHC molecule with unusual tissue distribution. *Nature* 351:485 (1991).

19. Gao, E. K., H. Kosaka, C.D. Surh, and J. Sprent. T cells contact with Ia antigens on nonhemopoietic cells in vivo can lead to immunity rather than tolerance. *J. Exp. Med.* 174:435-446 (1991).

20. Sprent, J., M. Schaefer, M. Hurd, C. D. Surh, and Y. Ron. Mature murine B and T cells transferred to SCID mice can survive indefinitely and many maintain a virgin phenotype. *J. Exp. Med.* 174:717-728 (1991).

21. Surh, C. D. and J. Sprent. Long-term xenogeneic chimeras: Full differentiation of rat T and B cells in SCID mice. *J. Immunol.* 147:2148-2154 (1991).

22. Frey, H. B. Ernst, C. D. Surh, and J. Sprent. Thymus-grafted SCID mice show transient thymopoiesis and limited depletion of $V\beta11^+$ T cells. *J. Exp. Med.* 175:1067-1071(1992).

23. Surh, C. D., E. K. Gao, H. Kosaka, D. Lo, C. Ahn, D. Murphy, L Karlsson, P. Peterson, and J. Sprent. Two subsets of epithelial cells in the thymic medulla. *J. Exp. Med.* 176:495-505 (1992).

24. Surh, C. D., B. Ernst, and J. Sprent. The growth of epithelial cells in the thymic medulla is under the control of mature T cells. *J. Exp. Med.* 176:611-616 (1992).

25. Kosaka, H., C.D. Surh, and J. Sprent. Stimulation of mature unprimed $CD8^+$ T cells by semi-professional APC in vivo. *J. Exp. Med.* 176:1291-1302(1992).

26. Karlsson, L., C. D. Surh, J. Sprent, and P. A. Peterson. An unusual class II molecule. *Immunology Today* 13:469-470(1992).

27. Leung, P.S., S. Krams, S. Munoz, C. D. Surh, A. Ansari, T. Kenny, D. L. Robbins, J. Fung, T. E. Starzl, W. Maddrey, R. L. Coppel, and M. E. Gershwin. Character-ization and epitope mapping of human monoclonal antibodies to PDC-E2, the

immunodominant autoantigen of primary biliary cirrhosis. *J. Autoimmunity* 5:703-718(1992).

28. Surh, C. D., J. Sprent, and S. R. Webb. Exclusion of circulating T cells from the thymus does not apply in the neonatal period. *J. Exp. Med.* 177:379-385(1993).

29. Van de Water, J., J. Turchany, P. S. C. Leung, J. Lake, S. Munoz, C. D. Surh, R. Coppel, A. A. Ansari, Y. Nakanuma, and M. E. Gershwin. Molecular mimickery in primary biliary cirrhosis: evendence for biliary epithelial expression of protein crossreactive with PDC-E2. *J. Clin. Invest.* 91:2653-2664(1993).

30. Sprent, J., H. Kosaka, E.-K. Gao, C. D. Surh, and S. R. Webb. Intrathymic and extrathymic tolerance in bone marrow chimeras. *Immunol. Rev.* 133:151-176(1993).

31. Surh, C. D. and J. Sprent. Anatomy and histology of the thymus. In: Intrathymic Development of T cells, J. Nikolic-Zugic ed., R. G. Landes Co., TX. pp3-27 (1994).

32. Surh, C. D., D. P. Gold, S. Wiley, D. B. Wilson, and J. Sprent. Rat T cell response to superantigens. I. Vß-restricted clonal deletion of rat T cells differentiating in rat → mouse chimeras. *J. Exp. Med.* 179:57-62 (1994).

33. Gold, D. P., C. D. Surh, K. S. Sellins, K. Schroder, J. Sprent, and D. B. Wilson. Rat T cell response to superantigens. II. Allelic differences in Vß8.2 and Vß8.5 ß chains determine responsiveness to staphylococcal enterotoxin B and mouse mammary tumor virus encoded products. *J. Exp. Med.* 179:63-69 (1994).

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